IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 18-651-CFC
TEVA PHARMACEUTICALS USA, INC., et al.	)	**CONSOLIDATED**
Defendants.	)	

DEFENDANTS' OPENING POST-TRIAL BRIEF

Thomas Francella (No. 3835)
Kaan Ekiner (#5607)
COZEN O'CONNOR
1201 North Market Street, Suite 1001
Wilmington, DE 19801
(302) 295-2025
tfrancella@cozen.com
kekiner@cozen.com
Attorneys for Defendants Apotex Inc. and Apotex Corp.

John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

OF COUNSEL:
Barry P. Golob
W. Blake Coblentz
Aaron S. Lukas
COZEN O'CONNOR
1200 Nineteenth Street N.W.
Washington, DC 20036
(202) 912-4800

Keri L. Schaubert
COZEN O'CONNOR
3 WTC, 175 Greenwich Street, 55th Fl.
New York, NY 10007
(212) 509-9400

Dated: April 26, 2022

OF COUNSEL:
J.C. Rozendaal
Deirdre M. Wells
William H. Milliken
Sasha Rao
Michael Bruns
Byron L. Pickard
STERNE, KESSLER, GOLDSTEIN
& FOX P.L.L.C.
1100 New York Avenue, N.W., Suite 600
Washington, DC 20005
(202) 371-2600

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

INTRODUCTION

This case concerns Vanda's efforts to prolong its market exclusivity on tasimelteon (brand name Hetlioz), a drug used to treat Non-24 hour sleep-wake disorder. Non-24 is a circadian rhythm sleep disorder typically affecting blind individuals that is characterized by a misalignment between the circadian drive to sleep and the normal 24-hour day. Bristol Myers Squibb synthesized tasimelteon in the late 1990s and, in 1999, obtained a patent covering both the tasimelteon compound and the use of tasimelteon to treat circadian rhythm sleep disorders. That patent, which Vanda licensed in 2004 and the validity of which Defendants have conceded, has protected Hetlioz from competition since its FDA approval in 2014, and it will continue to do so until it expires in December of this year.

Vanda, however, not content with its nearly two-decade monopoly on tasimelteon, sued Defendants for infringement of several follow-on patents that claim priority to applications filed in 2012, 2013, and 2014. The evidence at trial showed that Vanda simply waited too long to seek these follow-on patents. By 2012—thirteen years after BMS claimed tasimelteon and methods of using it to treat circadian rhythm sleep disorders—the prior art was replete with disclosures that either anticipated or rendered obvious the purported inventions claimed in the asserted follow-on patents.

Specifically as Dr. Emens—whom the Court found "very credible" and lacking "any source of bias," Tr. 1258:2-11—explained in detail, the claimed methods of treating non-24 by administering tasimelteon would have been obvious as of January 2012. Specifically, skilled artisans would have found it obvious to treat totally blind patients with Non-24 by administering tasimelteon once daily before bedtime; skilled artisans would have expected that such treatment could result in entrainment; and (since most people do not eat right before bed) it would have been obvious to administer tasimelteon "without food" as opposed to with food. Dr. Emens' testimony on these points—large swaths of which went completely unrebutted—demonstrates that claim 3 of the RE604 patent and claim 5 of the '487 patent are invalid.

The so-called "DDI patents" likewise claim the treatment of Non-24 with tasimelteon, and they add the requirement that the patient discontinue a strong CYP1A2 inhibitor (the '829 patent) or rifampin (the '910 patent) before administering tasimelteon. These additional limitations would have been obvious too, as Defendants' expert Dr. Greenblatt explained. Specifically, Dr. Greenblatt's testimony showed that skilled artisans would have found it obvious to discontinue treatment with a CYP1A2 inhibitor (*e.g.*, fluvoxamine, ciprofloxacin, or verapamil) or a CYP3A4 inducer (*i.e.*, rifampin) before treating a patient with tasimelteon in order to avoid a drug-drug interaction.

The asserted patents are invalid, and the Court should grant judgment in Defendants' favor.[1]

ARGUMENT

I. The asserted claims of the method-of-treatment patents are invalid as obvious.

A. State of the art as of the priority date

1. The prior art taught that exogenous melatonin could entrain totally blind Non-24 patients to a 24-hour sleep-wake cycle by effecting phase shifts via its activity at the body's melatonin receptors.

By January 2012, the concept of "entraining" a person suffering from a circadian rhythm sleep disorder (such as Non-24) by resetting their internal circadian rhythm was nothing new. As Dr. Emens explained, by that point decades of research had established exogenous melatonin's ability to treat patients with circadian rhythm sleep disorders by synchronizing their misaligned biological clocks to a normal 24-hour day. Tr. 708:16-709:22, 712:12-723:13 (Emens). Skilled artisans knew that this synchronization was accomplished by "phase shifting" the biological clock by a certain amount each day. Tr. 708:16-709:22. And skilled artisans had pinned down the precise mechanism by which melatonin

[1] Vanda also asserted claim 10 of U.S. Patent No. 10,829,465 against Defendants, but has dismissed with prejudice its allegations that Defendants infringe that patent. *See* D.I. 310.

achieved this effect: it binds to the brain's melatonin MT1 and MT2 receptors. Tr. 709:23-710:3.

Dr. Emens cited a wealth of prior-art literature in support of his testimony. As early as 1995, researchers concluded that "[m]elatonin is able to phase-shift the endogenous circadian clock." JTX-139.1 (Deacon & Arendt 1995). That same paper noted that melatonin had already "been used extensively in the treatment of circadian rhythm disorders." JTX-139.7; *see* Tr. 713:14-23 (Emens). Five years later—and more than a decade before the priority date—researchers from two separate sleep labs independently published studies proving that administration of exogenous melatonin could entrain totally blind patients suffering from Non-24. *See* JTX-147.1 (Lockley 2000) ("These results show for the first time that daily melatonin administration can entrain free-running circadian rhythms in some blind subjects."); JTX-148.1 (Sack 2000) ("Administration of melatonin can entrain circadian rhythms in most blind people who have free-running rhythms."); Tr. 714:16-716:1 (Emens).

Indeed, as Dr. Emens explained, by the early 2000s, melatonin's ability to entrain Non-24 patients was so well established that researchers—including Dr. Emens himself—had shifted their attention towards the *refinement* of treatment with melatonin, and specifically optimization of dose and timing of administration. *See* Tr. 716:2-720:4 (citing DTX-154 (Lewy & Emens 2001); JTX-123 (Lewy &

Emens 2002); DTX-155 (Lewy & Emens 2004); DTX-156 (Lewy & Emens 2005); JTX-146 (Hack 2003)). The prior art could hardly have been clearer: "[d]aily administration of exogenous melatonin is the current treatment of choice for this so-called 'non-24 h sleep/wake disorder.'" DTX-39.1 (Skene & Arendt 2007); *see* Tr. 720:3-721:4 (Emens); Tr. 483:6-15 (Feeney) (conceding that experts in the field would have agreed that, as of 2010, there was "strong and unequivocal evidence for the chronobiotic properties of melatonin"). Indeed, the art was so clear that, by 2007, the American Academy of Sleep Medicine's official practice parameters recommended the use of melatonin to treat Non-24. DTX-37.11 (Morgenthaler 2007); *see* Tr. 722:20-723:22 (Emens).[2]

These publications illustrate that, long before January 2012, skilled artisans had conclusively shown that melatonin, through its binding activity at the MT1 and MT2 receptors, could induce circadian phase shifts and thus successfully treat blind patients with non-24 by entraining them to a 24 hour sleep-wake cycle. To be sure, there was (and still is today) some dispute about the optimal dose and timing of administration of melatonin. *See, e.g.*, Tr. 723:7-9 (Emens); Tr. 917:25-920:4,

[2] Vanda adduced evidence at trial that some researchers were unsuccessful in achieving entrainment with melatonin in studies in the 1980s and 1990s. *See, e.g.*, Tr. 899:15-902:25 (Lockley). That is true, but irrelevant. The relevant point is that by 2000—more a *decade* before the priority date—those in the field knew that melatonin could in fact, entrain blind non-24 patients.

923:4-924:14 (Lockley). But—as Dr. Emens explained in unrebutted testimony—there was then and is now no dispute that it works. Tr. 723:7-13 (Emens).

2. The prior art taught that tasimelteon is a synthetic melatonin agonist with similar binding affinities for the melatonin receptors and could likewise phase-shift a person's circadian rhythm.

Melatonin, of course, was not the only melatonin agonist known in the art before the priority date. Tr. 709:18-22 (Emens). As Dr. Emens explained, at least by 1999 skilled artisans also knew about tasimelteon—a manmade melatonin agonist that could bind to the MT1 and MT2 receptors and, like melatonin, phase-shift a person's circadian rhythm. *Id.* at 709:18-710:3, 724:13-725:14; *see* JTX-12 (Catt 1999). Indeed, BMS's '529 patent—sometimes referred to at trial as "Catt"—claimed the use of tasimelteon *to treat circadian rhythm sleep disorders*. JTX-12.24 (claim 14).

The development timeline for tasimelteon closely mirrors that of melatonin; tasimelteon was only a handful of years behind. Three years after the landmark Lockley and Sack papers showed that melatonin could entrain blind patients with Non-24, a study of tasimelteon in animals concluded that tasimelteon was "a novel melatonin receptor agonist that may be a useful treatment for sleep disorders that result from disruption of circadian rhythms" in humans. JTX-91.1 (Vachharajani 2003); *see* Tr. 725:5-726:11 (Emens). By 2007, *Vanda itself* had disclosed in a published patent application (the "'244 publication") that tasimelteon was a

"specific and potent agonist of the MT1[] and MT2[] receptors" in the human brain that "demonstrate[d] potent chronobiotic activity" in the human body—*i.e.*, that could phase shift a person's internal circadian clock. DTX-41.2 ('244 publication); *see* Tr. 727:15-19 (Emens). Vanda concluded that, based on the available data on tasimelteon's phase-shifting properties, "[a]n oral dose of about 20 to about 50 mg is effective in treating sleep disorders when administered about 1/2 hour before sleep time." DTX-41.24; *see* Tr. 727:15-22 (Emens). And the '244 publication in fact contains claims—claims that closely mirror the ones Vanda is asserting in this case—directed to a method of treating circadian rhythm sleep disorders by administering 20 mg tasimelteon 0.5 hours before a patient's bedtime. DTX-41.25–26; *see* Tr. 727:23-728:6 (Emens).

Research papers and review articles that followed the '244 publication reiterated the growing consensus that tasimelteon had strong binding affinities for the MT1 and MT2 receptors and the ability to phase-shift. *See, e.g.*, DTX-16.1 (Hardeland 2009); DTX-20.6 (Lankford 2011); *see* Tr. 728:7-730:23, 798:11-800:2 (Emens). Many of these references drew explicit comparisons between tasimelteon and melatonin and reasoned that, because tasimelteon operated via a similar mechanism of action, it likely posed similar entraining potential. For example, Hardeland noted that tasimelteon's phase-shifting properties were "*expected* from a melatonergic drug, and are also observed with melatonin and synthetic melatonin

agonists." DTX-16.7 (emphasis added); *see* Tr. 730:14-23 (Emens). Vanda's own CEO concluded in a 2009 article that "a phase-shifting drug, such as tasimelteon, has therapeutic potential for circadian rhythm sleep disorders." Tr. 175:7-10 (Polymeropoulos). And Lankford observed in 2011 that "tasimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin" and "[t]herefore…should be especially well suited for treatment of CRSDs." DTX-20.6; *see* Tr. 799:16-24 (Emens); *see also* PTX-473.5 (Vanda 2011 10-K) (noting that tasimelteon "binds selectively to the brain's melatonin receptors, which are thought to govern the body's natural sleep/wake cycle," and that "[c]ompounds that bind selectively to these receptors are thought to be able to help treat sleep disorders").

3. The prior art disclosed the precise dosing regimen claimed in the asserted patents: administration of 20 mg tasimelteon to totally blind Non-24 patients 0.5–1.5 hours before bedtime.

As explained above, by January 2012 the prior art was quite clear that both tasimelteon and melatonin were effective in entraining patients with circadian rhythm sleep disorders. Even if that were *all* they knew, the obviousness case here would be compelling. But there is more: multiple prior-art references disclose the *exact dosing regimen* recited in the asserted claims.

The '244 publication, which predates the filing of the asserted patents by five years, includes claims to a method of treating circadian rhythm sleep disorders

(which would include Non-24) by administering 20 mg tasimelteon 0.5 hours before a patient's bedtime. DTX-41.25–26; *see* Tr. 727:23-728:6 (Emens). Then, in July 2010, Vanda posted its Phase III trial protocol for Hetlioz on clinicaltrials.gov, a publicly available government website. DTX-42; *see* Tr. 797:15-798:8 (Emens). The original posting (which the parties refer to by shorthand as "Clinical Trials") discloses administration of 20 mg tasimelteon to totally blind Non-24 patients one hour before bedtime. *See* DTX-42.9–10; Tr. 796:24-797:12 (Emens). The 2011 Lankford article refers to this trial and summarizes the protocol, *see* DTX-20.6, as does Vanda's 2011 10-K, which Dr. Polymeropoulos admitted was available to the public before 2012. Tr. 176:23-25 (Polymeropoulos); *see* PTX-473.6.

In short, the prior art not only disclosed the general idea that tasimelteon was likely to be useful in treating Non-24 at the claimed dose; it disclosed the specific dosing regimen recited in the asserted claims.

4. The prior art disclosed avoiding drug-drug interactions with the CYP450 family of enzymes, and specifically CYP1A2 and CYP3A4.

There were extensive teachings in the prior art concerning the need to avoid drug-drug interactions. As Dr. Greenblatt testified, a skilled artisan would have known that the cytochrome P450 ("CYP450") family of enzymes plays an important role in drug metabolism (and therefore potential drug-drug interactions), Tr. 1030:5-1031:6 (Greenblatt); Tr. 1147:17-24 (Parkinson); *see also* DTX-9

(Badyal 2001); JTX-95 (Lynch 2007), and that six to eight CYP enzymes are responsible for the metabolism of nearly 90% of drugs. Tr. 1031:18-25 (Greenblatt); Tr. 1147:7-13, 1147:25-1148:5 (Parkinson); *see* JTX-95.1; DTX-9.2. As Dr. Greenblatt further testified, a skilled artisan would have also known that CYP3A4 is of particular importance because it is the only CYP enzyme located in both the intestine and the liver, and because it metabolizes nearly half of all drugs used in clinical practice, either partially or entirely. Tr. 1032:1-15, 1053:23-1054:5 (Greenblatt); Tr. 1146:19-1147:6 (Parkinson); *see* DTX-9.1.

A skilled artisan also would have been aware, as Dr. Greenblatt explained, of FDA's requirements for in vitro testing of all new drugs in order to identify the enzymes that contribute to drug metabolism, Tr. 1032:23-1033:3, 1033:14-22 (Greenblatt), which includes testing for metabolism by CYP1A2 and CYP3A4, Tr. 1148:6-11 (Parkinson). Indeed, FDA requires in vitro testing as a first step in determining the possibility of a drug-drug interaction ("DDI"). Tr. 1033:14-22 (Greenblatt).

As Dr. Greenblatt explained, a POSA would have known that DDIs can occur when two drugs (*e.g.*, Drug X and Drug Y) are co-administered and Drug X acts on CYP enzymes to increase or decrease the metabolism of Drug Y. Tr. 1041:3-10 (Greenblatt).

On one hand, when Drug X *inhibits* the activity of CYP enzymes that metabolize Drug Y, this results in reduced Drug Y metabolism and increased plasma concentrations of Drug Y. Tr. 1041:3-15 (Greenblatt). Such drugs are known as "CYP inhibitors," and prior-art references such as Ogu, Badyal, and Lynch disclosed many known examples. Tr. at 1042:9-23 (Greenblatt); *see* DTX-24.2 (Ogu 2000), DTX-9.5, JTX-95.3. Specifically, Dr. Greenblatt testified, and Vanda's expert Dr. Parkinson confirmed, that it was common knowledge that fluvoxamine was one of the, if not the, strongest known inhibitor of CYP1A2. Tr. 1043:3-9 (Greenblatt); Tr. 1149:3-7 (Parkinson).

On the other hand, when Drug X *induces* the expression of CYP enzymes that metabolize Drug Y, this results in increased Drug Y metabolism and decreased plasma concentrations of Drug Y. Tr. 1041:3-21 (Greenblatt). Such a drug is called a "CYP inducer," and prior-art references such as Ogu, Badyal, and Lynch disclosed many known inducers of CYP enzymes. Tr. 1042:9-23 (Greenblatt); *see* DTX-24.2; DTX-9.4, 9.5; JTX-95.3. As Dr. Greenblatt testified, and Dr. Parkinson confirmed, it was common knowledge that rifampicin (*i.e.*, rifampin) was the strongest known inducer of CYP3A4. Tr. 1043:10-17 (Greenblatt); Tr. 1148:18-22 (Parkinson). Further, Dr. Parkinson confirmed that a skilled artisan would have been aware that for any new drug, possible DDIs can be predicted even before the

drug reaches the clinical phase of development. Tr. 1149:8-1150:14 (Parkinson); *see* DTX-9.7.

5. The prior art disclosed that tasimelteon was metabolized by CYP1A2 and thus coadministration of tasimelteon with a CYP1A2 inhibitor should be avoided.

By 2012, the prior art was clear that tasimelteon is metabolized by CYP1A2. As Dr. Greenblatt explained, Vachharajani[3] discloses that tasimelteon is metabolized by CYP1A2 in vitro. JTX-91.10 (Vachharajani 2003) ("In studies with microsomes overexpressing specific human CYP isoforms, BMS-214778 [tasimelteon] was primarily metabolized by…[CYP]1A2…The percentages of parent compound remaining after 3 h of incubation with the four isoforms that metabolized BMS-214778 [tasimelteon] were…1A2: 27%...."); Tr. 1036:3-16, 1100:2-9 (Greenblatt). Likewise, Hardeland, a review article published six years after Vachharajani, reiterated that "tasimelteon was primarily metabolized by the CYP1A2… isoenzymes[]." DTX-16.4 (citing Vachharajani); Tr. 1036:3-16, 1049:16-20, 1100:2-9 (Greenblatt). These publications confirm that, by January 2012, skilled artisans knew that CYP1A2 plays a role in tasimelteon's metabolism. Indeed, Dr. Parkinson confirmed that *Vanda itself* cited Vachharajani as evidence that CYP1A2 is one of the major CYP enzymes involved in the metabolism of

[3] Dr. Greenblatt referred to Vachharajani (JTX-91) as the Bristol-Meyers Squibb publication because the authors were from BMS. *See, e.g.*, Tr. 1036:3-16 (Greenblatt); *see also* Tr. 1112:13-21 (Court).

tasimelteon. Tr. 1159:20-1160:23 (Parkinson); JTX-150.2 ("Early in vitro studies suggested that cytochrome P450 (CYP)…1A2…[was among] the major CYP enzymes involved in the metabolism of tasimelteon…."), JTX-150.4.

Further, not only did the prior art disclose that tasimelteon is metabolized by CYP1A2, but Hardeland specifically taught that because "tasimelteon is metabolized by the CYP isoenzymes 1A2…coadministration of any drug that inhibits one of these isoenzymes *should be regarded with caution*." DTX-16.6 (emphasis added); Tr. 1049:16-1050:9 (Greenblatt).

6. The prior art taught that ramelteon—a melatonin receptor agonist similar to tasimelteon—was metabolized by CYP1A2 and CYP3A4 and thus inhibitors of CYP1A2 and inducers of CYP3A4, specifically, rifampin, should not be coadministered with ramelteon.

Tasimelteon was not the only synthetic melatonergic agent known in the prior art before the priority date. Tr. 1037:5-6[4] (Greenblatt); DTX-16.2; JTX-93.1-93.2 (Pandi-Perumal 2011). As Dr. Greenblatt explained, by 2012, skilled artisans also knew about ramelteon—a manmade melatonin agonist "closely related to tasimelteon." Tr. 1037:6. Indeed, like tasimelteon, ramelteon was known to bind to, and have high affinity for, melatonin MT1 and MT2 receptors. JTX-35.1

[4] The transcript (Tr. 1037:4) incorrectly refers to Ms. Young—as opposed to Mr. Lukas—as the attorney conducting the direct examination. Likewise, the question posed at Tr. 1037:6 ("What is ramelteon Dr. Bergmeier?") incorrectly references Dr. Bergmeier, as opposed to Dr. Greenblatt.

(Rozerem (ramelteon) label); DTX-16.3; JTX-93.2; JTX-92.2 (Obach 2010); Tr. 1035:7-18, 1037:5-14, 1040:6-17 (Greenblatt). Further, the prior art taught that both tasimelteon and ramelteon have relatively short half-lives. Tr. 1040:6-19 (Greenblatt). Hardeland also taught that tasimelteon and ramelteon are structurally similar, sharing a dihydrobenzofuran structure and the propanamide residue. DTX-16.3-16.4 ("Ramelteon exhibits structural similarity to tasimelteon, as these compounds share the dihydrobenzofuran structure and the propanamide residue."); Tr. 1040:6-22 (Greenblatt).

Much was also disclosed in the prior art about the metabolism of ramelteon. JTX-93; JTX-35; JTX-92. For example, numerous references, including Pandi-Perumal, the Rozerem label, and Obach taught that ramelteon is metabolized by CYP1A2 and CYP3A4. JTX-93.4; JTX-35.2, 35.10; JTX-92.1; Tr. 1038:25-1039:13, 1040:6-24 (Greenblatt); Tr. 1156:6-10 (Parkinson). Further, many of these same references cautioned against co-administration of ramelteon with a CYP1A2 inhibitor or CYP3A4 inducer, given the known metabolic pathway of ramelteon, and known drug-drug interactions. JTX-93.4; JTX-35.8, 35.10. And, while Vachharajani states that metabolism of tasimelteon by CYP3A4 was not detected, JTX-91.10, Dr. Greenblatt explained that "[t]he interaction can't be excluded because induction causes a massive increase in the amount of enzymes,

and you cannot exclude a major role of CYP3A4 in the induced state even if you can't detect it in the uninduced state." Tr. 1116:8-20 (Greenblatt).

Dr. Greenblatt testified that a skilled artisan would have known that fluvoxamine—a CYP1A2 inhibitor—interacts with ramelteon. Tr. 1043:18-20, 1116:24-1117:13 (Greenblatt); DTX-28.9 (von Moltke 2010); JTX-93.4; JTX-92; JTX-35.10. In fact, as Dr. Greenblatt explained, co-administration of ramelteon and fluvoxamine results in a greater than 100-fold increase in the plasma concentration of ramelteon. Tr. 1043:18-1045:23 (Greenblatt); DTX-28.9; JTX-93.4; JTX-35.10. Because of this interaction, the prior art—including Pandi-Perumal and the Rozerem label—explicitly state that ramelteon should not be used in combination with certain CYP1A2 inhibitors, including fluvoxamine and ciprofloxacin. JTX-93.4; JTX-35.8, 35.10; Tr. 1045:3-1046:3, 1116:24-1117:13 (Greenblatt).

Dr. Greenblatt also testified that a skilled artisan would have known that rifampin—the strongest known CYP3A4 inducer—interacts with ramelteon. Tr. 1043:10-17, 1046:5-7, 1116:24-1117:13 (Greenblatt); JTX-93.4; JTX-35.10. For example, the Rozerem label discloses that co-administration of ramelteon and rifampin results in an 80% decrease in the plasma concentration of ramelteon. JTX-35.10; Tr. 1046:5-21, 1116:24-1117:13 (Greenblatt). Because of this interaction, the prior art—including Pandi-Perumal and the Rozerem label—warns

that the efficacy of ramelteon may be reduced if ramelteon and rifampin are co-administered together and thus coadministration should be avoided. JTX-93.4; JTX-35.10; Tr. 1046:5-1047:5, 1116:24-1117:13 (Greenblatt).

Given the explicit disclosures in the prior art concerning the similarities between tasimelteon and ramelteon, and the wealth of information concerning the metabolism of ramelteon and its known drug-drug interactions, there can be no doubt—as Dr. Greenblatt testified—that a POSA would have looked to ramelteon as relevant to understanding possible DDIs for tasimelteon and thus would have been concerned about a DDI between tasimelteon and rifampin. Tr. 1037:5-14; 1040:6-24; 1047:23-1048:19, 1050:20-1052:2 (Greenblatt).

B. Claim 3 of the RE604 patent is invalid.

Claim 3 of the RE604 patent claims a method of treating a totally blind patient with Non-24 by entraining that patient with tasimelteon. As explained above, skilled artisans knew long before 2012 that melatonin agonists like tasimelteon could treat blind Non-24 patients by resetting their biological clocks so that they followed a conventional sleep-wake cycle. Skilled artisans even knew the mechanism by which this therapeutic outcome is achieved: melatonin agonists bind to the MT1 and MT2 receptors in the brain, which allows the compound to phase-shift a person's circadian clock, thereby aligning a person's clock with a normal sleep schedule. Prior-art reference after prior-art reference disclosed that, like

melatonin, tasimelteon exhibited strong binding affinities for the MT1 and MT2 receptors and could phase-shift a person's circadian rhythm. And these same references concluded that tasimelteon—administered at the claimed dose, at the claimed time—was an attractive treatment option for circadian rhythm sleep disorders generally and Non-24 specifically. Indeed, Vanda itself tried to patent this treatment regimen in an application published in 2007. Only *five years later* did Vanda attempt to obtain the claims it now accuses Defendants of infringing.

The bottom line is this: Vanda waited too long to seek patent protection. The method it has attempted to monopolize was disclosed—or at the very least made obvious—long before January 2012. The Court should hold the claim invalid.[5]

1. Claim 3 is invalid as obvious over two combinations of prior art: Lankford, Hack, and the '244 publication; and Hardeland, Hack, and the '244 publication.

As Dr. Emens explained, at least two combinations of references contain all of the limitations of asserted claim 3 of the RE604 patent: Lankford, Hack, and the '244 Publication; and Hardeland, Hack, and the '244 Publication. Tr. 803:8-809:21, 811:18-813:13 (Emens). And a skilled artisan would have been motivated

[5] An obviousness analysis typically involves as assessment of "the level of ordinary skill in the pertinent art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Here, however, the parties have stipulated that, with respect to invalidity of the method-of-treatment patents, "each expert's opinion would be the same using either definition of a person of ordinary skill in the art." D.I. 299 ¶ 4. Accordingly, the Court need not resolve any dispute over the level of ordinary skill in the art.

to combine these references with a reasonable expectation of success. *See* Tr. 809:22-811:16, 813:14-815:7. The Court should therefore find the claims obvious. *See Nalpropion Pharms. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344, 1355 (Fed. Cir. 2019) (affirming obviousness ruling where "every limitation in the claims at issue was met by" defendant's prior art combination).

(a) Each limitation of claim 3 is found in the asserted prior-art combinations.

(i) "a method of entraining a patient suffering from Non-24 to a 24-hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of 7-9 hours"

Dr. Emens showed that the first limitation of claim 3—the "entraining" limitation—is either suggested or expressly taught by all four references in the two prior-art combinations. Tr. 803:7-16 (Emens).

Lankford discloses that tasimelteon's "high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin," and its "already demonstrated" circadian phase-resetting effects would make it "especially well suited for treatment" of circadian rhythm sleep disorders. DTX-20.6. Lankford also discloses that the drug was being tested in blind Non-24 patients. *Id.* Both disclosures would have suggested to a skilled artisan that tasimelteon can "reset[] the time of the circadian pacemaker," which is "the mechanism by which you achieve entrainment." Tr. 803:17-804:3 (Emens). This conclusion is particularly

evident in light of Dr. Emens' testimony that only two "treatment" strategies for circadian rhythm disorders were known before 2012: entraining the patient with a melatonin agonist or putting them to sleep at the desired time with a sedative hypnotic. Tr. 708:16-709:3. Given that knowledge, it would have been obvious to skilled artisans that Lankford was referring to treating patients with tasimelteon *via entrainment*. *See* Tr. 803:17-804:3; *cf Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1049 (Fed. Cir. 2019) ("in determining obviousness, all references are assessed 'on the basis of what they reasonably disclose and suggest to one skilled in the art'") (quoting *In re Aslanian*, 590 F.2d 911, 914 (C.C.P.A. 1979)).[6]

Hack explicitly discloses entraining Non-24 patients to a normal 24 hour sleep-wake cycle by using melatonin. JTX-146.1 ("Exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects."); *see* Tr. 804:8-805:5 (Emens). Hack also discloses that Non-24 patients who received melatonin slept an average of 6.6 hours per night, with a standard

[6] While Vanda may argue otherwise, *cf.* Tr. 877:25-878:5 (Emens), a reference need not explicitly incant the word "entrainment" to render this limitation obvious. Skilled artisans are not automatons; they interpret prior-art disclosures based on their background knowledge in the relevant field. *See Aslanian*, 590 F.2d at 914. That is precisely what Dr. Emens did. *See, e.g.*, Tr. 803:17-805:17 (Emens).

deviation of 1.1 hours—in other words, approximately 7 to 9 hours. JTX-146.6 (Table 3).[7]

The ’244 publication, in turn, discloses that tasimelteon can “regulate circadian rhythms, including the sleep/wake cycle,” DTX-41.2, which a skilled artisan “would take to mean the mechanism by which you achieve entrainment for the treatment of a circadian rhythm disorder” like Non-24. Tr. 805:6-13 (Emens); *see also* DTX-41.25 (claiming the use of tasimelteon to treat circadian rhythm sleep disorders). The ’244 publication also states that tasimelteon had “demonstrate[d] *potent chronobiotic activity* in preclinical models of acute phase-shifting and chronic *re-entrainment*.” DTX-41.2 (emphases added).

Finally, Hardeland notes that tasimelteon had been shown to be effective “in resetting the circadian melatonin rhythm…which indicated its potential suitability as treatment for…circadian rhythm sleep disorders.” DTX-16.1. This, again, would have suggested to a skilled artisan the concept of entrainment, since that phase-

[7] As the Court heard at trial, the parties dispute the meaning of “daily sleep period.” *See, e.g.*, Tr. 802:2-803:6 (Emens). Dr. Emens explained that a skilled artisan would interpret this to mean a period in which “a person was mostly asleep,” whereas Vanda contends that the term merely requires that the person experience “increased sleepiness.” *See id.* The Court need not resolve this dispute for purposes of invalidity, however, because Hack discloses the limitation under either interpretation. The patients in Hack who slept an average of 6.6 hours (by definition) experienced a period of “increased sleepiness” lasting at least that long.

shifting is the mechanism by which entrainment is achieved. Tr. 811:24-812:12 (Emens).

(ii) "maintaining said 24-hour sleep-wake cycle"

The second limitation of the asserted claims—"maintaining" the 24 hour sleep-wake cycle"—is taught by both Hack and the '244 publication. Hack discloses that "chronic usage of melatonin is necessary for free-running blind people to remain entrained to the 24-h day," JTX-146.2, and the '244 publication similarly instructs that treatment of circadian rhythm disorders with tasimelteon "can continue for some time" after a "patient's circadian rhythm is restored to normal" to "lessen the likelihood of relapse," DTX-41.5-6. Dr. Emens explained that these passages would teach the RE604 patent's "maintaining" limitation because they indicate "that to avoid relapse, that treatment needs to continue for some time, which I would say is synonymous with maintaining the treatment." Tr. 805:18-806:11.

(iii) "orally administering to the patient 20 mg of tasimelteon"

Lankford, the '244 publication, and Hardeland repeatedly disclose the dosing limitation: "orally administering…20 mg of tasimelteon." Specifically, Lankford notes that the blind Non-24 patients in Vanda's Phase III trial were receiving 20 milligram doses. DTX-20.6; *see* Tr. 806:12-22 (Emens). Lankford also discloses other clinical trials where researchers administered doses of

tasimelteon ranging from 10-100 mg to healthy volunteers and insomnia patients. DTX-20.5.

The ’244 publication likewise describes the prior-art insomnia studies involving dose ranges of tasimelteon including 20 mg, DTX-41.9-24, and it concludes that “[a]n oral dose of about 20 to about 50 mg [tasimelteon] is effective in treating sleep disorders,” DTX-41.24. And the claims of the ’244 publication recite administration of “about 20 to about 50 mg” tasimelteon per day. DTX-41.25 (claim 6); *see* Tr. 806:23-807:4 (Emens). Hardeland, based on its own review of the tasimelteon literature, concludes effectively the same thing: “The most effective doses of tasimelteon were in the range of 20 to 50 mg/day.” DTX-16.7; *see* Tr. 812:13-23 (Emens). Moreover, as Dr. Emens explained, a skilled artisan would have been particularly likely to select the 20 mg dose because “you’d want the lowest effective dose that’s not going to give you side effects. Or at least minimize side effects.” Tr. 807:5-9.

(iv) “0.5 to 1.5 hours before the target bedtime”

Lankford, the ’244 publication, and Hardeland also disclose the claimed timing of administration: “0.5 to 1.5 hours before the target bedtime.” As noted above, all three references discuss the studies of tasimelteon in insomnia and note that the tasimelteon was administered 30 minutes before the subject’s target bedtime. *See* DTX-20.5 (Lankford); DTX-41.10 (’244 publication); DTX-16.5-6

(Hardeland); Tr. 807:13-808:20, 812:24-813:9 (Emens). And Vanda's '244 publication claims administration of 20-50 mg tasimelteon administered 0.5 hours before bedtime to treat circadian rhythm sleep disorders. *See* DTX-41.25-26 (claims 8–9); Tr. 808:10-20 (Emens). As Vanda's expert Dr. Czeisler admitted, administration of tasimelteon shortly before bedtime was desirable because it would "take advantage of the soporific effect the drug has." Tr. 1211:2-6 (Czeisler).

(v) "wherein the patient is totally blind"

Lastly, both Lankford and Hack disclose treatment of a "totally blind" Non-24 patient. Tr. 808:21-809:16 (Emens). As said, Lankford discusses Vanda's Phase III clinical trial for tasimelteon and notes that the patients in the trial were totally blind (that is, had no light perception) and had Non-24. DTX-20.6; *see* Tr. 809:2-9 (Emens). Hack, for its part, plainly states that the patients being treated in that study were blind individuals suffering from "free-running" circadian rhythms—that is, Non-24. JTX-146.1; *see* Tr. 708:13-15, 809:10-16 (Emens).

(b) A skilled artisan would have been motivated to combine the asserted references to arrive at the claimed invention and would have had a reasonable expectation of success in doing so.

A skilled artisan would find a motivation to combine Lankford and Hardeland, respectively, with Hack and the '244 publication by reading the references themselves. And those references on their face provided skilled artisans

with every expectation of success in arriving at the invention claimed in the RE604 patent.

Specifically, as Dr. Emens explained, having read Hack, a skilled artisan would know that melatonin could entrain blind people with Non-24 such that they could achieve a consistent sleep period of approximately 7 to 9 hours. Tr. 809:22-810:7, 813:14-21. And Lankford, Hardeland, and the '244 Publication would inform the skilled artisan that tasimelteon (1) "act[ed] on the same types of receptors" as melatonin; (2) exhibited "the exact same mechanism [of] action" that gave melatonin its ability to entrain (that is, "reset[ting] the timing of the biological clock" by causing phase shifts); and (3) would likely "be an effective treatment for…numerous circadian rhythm sleep disorders, such as Non-24." Tr. 809:22-814:19; 813:14-814:3. Connecting the dots from melatonin to tasimelteon would require no leap of inventiveness. Lankford, Hardeland, and the '244 publication explicitly connect the dots themselves:

- Lankford: "[T]asimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin. Therefore, *tasimelteon should be especially well suited for treatment of CRSDs* [circadian rhythm sleep disorders]…. Tasimelteon has already demonstrated its circadian phase-resetting effects." DTX-20.6 (emphasis added).
- '244 publication: "MA-1 [tasimelteon] is a specific and potent agonist of the MT1R and MT2R melatonin receptors in the…region of the brain associated with the biological clock. Engagement of these receptors by melatonin is believed to regulate circadian rhythms, including the sleep/wake cycle." DTX-41.2. (citation omitted)

- Hardeland: Tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders…or other types of entrainment difficulties. *These properties are expected from a melatonergic drug, and are also observed with melatonin*." DTX-16.7 (emphasis added).

Vanda's own witnesses acknowledged the close link between melatonin and tasimelteon. Dr. Lockley stated that melatonin's ability to "entrain the circadian rhythms of blind people" was "what led to the thinking that tasi[melteon] might be effective." Tr. 935:3-17 (Lockley); *see* DTX-331.3; Tr. 471:22-473:3 (Dressman). Dr. Czeisler told the FDA that melatonin's success was "inspirational" for the development of tasimelteon. Tr. 1208:11-1210:4 (Czeisler); *see* PTX-263.30. And one of the inventors on the patents agreed that Vanda used the prior-art melatonin studies to inform "many of the important design elements" of the Hetlioz clinical trials. Tr. 468:12-24 (Dressman).

It bears repeating, moreover, that, by 2007, Vanda had actually attempted to claim the treatment of circadian rhythm disorders by administering tasimelteon according to the exact dosing regimen claimed here: 20 mg administered approximately 0.5 hours before bedtime. DTX-41.25-26 ('244 publication); *see also* Tr. 482:16-19 (Feeney). Vanda's own prior art thus evidences the motivation to arrive at the claimed invention, as well as the expectation of success. *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1029 (Fed. Cir. 2018) (relying on the plaintiff's prior-art patent application, which disclosed administering the drug at

issue in the claimed 40 milligram dose, as evidencing a reasonable expectation of success that the claimed dose reduced side effects).[8]

A skilled artisan would have also known from Lankford, Clinical Trials, and Vanda's 2011 10-K that Vanda was in the process of seeking FDA approval to treat blind Non-24 patients with tasimelteon. *See* DTX-20.6 (Lankford); DTX-42.9-10 (Clinical Trials); PTX-473.6 (Vanda 2011 10-K); Tr. 176:23-25 (Polymeropoulos). This real-world fact, Dr. Emens explained, would have telegraphed to a skilled artisan that those exploring treatment options for Non-24 in the blind considered the evidence on tasimelteon compelling enough to justify "spending the time and money to do a big Phase 3 clinical trial," which "clearly" meant "there was a reasonable expectation that they [we]re going to succeed" in proving that the drug could treat the disorder. Tr. 811:6-16 (Emens).

[8] Vanda may argue that the 20 mg dose administered shortly before bedtime was not obvious because skilled artisans would have worried about the "spillover" phenomenon—that is, the possibility that the tasimelteon might stay in the patient's system long enough to cause a phase delay that might counteract the desired phase advance. *See, e.g.*, Tr. 1180:8-25 (Czeisler). That argument fails because, as Dr. Emens explained, 20 mg *had already been shown to work*—"[s]o if 20 milligrams causes spillover, whatever spillover it caused wasn't enough to negate the phase shift that it caused." Tr. 883:20-884:22 (Emens). "In other words, spillover is an explanation you make afterwards to explain the magnitude of the phase shift you got." *Id.* And Vanda's expert Dr. Czeisler admitted that there were no prior-art studies that explicitly raised spillover as a concern with tasimelteon. *See* Tr. 1199:2-6 (Czeisler). Vanda's spillover arguments are, in effect, a hindsight attempt to explain why a skilled artisan's expectation of success might have been wrong.

To be sure, as of January 2012, the *results* of the Phase III trial were not public, so a skilled artisan would not have known with absolute certainty that the claimed treatment method was effective in entraining Non-24 patients. But that is not the standard for obviousness. "[T]he standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA," *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1192 (Fed. Cir. 2019) (quoting lower court with approval), and a "[reasonable] expectation of success need only be reasonable, not absolute," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). The question is not whether there existed in the prior art data sufficient to prove safety and efficacy to the FDA; the question is merely whether a skilled artisan would have reasonably expected the claimed method to work. *See* Tr. 1198:23-1199:1 (Czeisler); *Nalpropion*, 934 F.3d at 1354 ("[W]hile bupropion alone may not have been entitled to FDA approval as a weight-loss treatment, '[t]here is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval.'") (quoting *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013)). Defendants have met the applicable standard here.

(c) There was no long-felt need for an effective treatment for Non-24 in the blind as of 2012.

Vanda's argument that the claimed invention "met a long felt but previously unmet medical need," Tr. 1186:3-7 (Czeisler), fails. There was no long-felt need for a drug that could entrain blind patients with Non-24 for a very simple reason: by 2003, skilled artisans knew that melatonin could do exactly that. Tr. 1217:7-1218:21 (Emens); *see BTG Int'l Ltd. v. Amneal Pharms. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019) (evidence failed to establish long-felt need for prostate cancer treatment because "other treatments for prostate cancer were available").

Indeed, even now, melatonin remains the standard treatment option over tasimelteon for those suffering from Non-24. Dr. Emens, who treats Non-24 as part of his work at the VA, testified that the VA health system—"the largest fully integrated healthcare system in th[e] country"—lists melatonin on its formulary for the treatment of Non-24. Tr. 1219:16-1220:15 (Emens). Tasimelteon, on the other hand, is nowhere to be found. Tr. 1220:2-6.

2. If the Court finds that Defendants' labels induce infringement of claim 3, Vanda's substantively identical clinical trial protocol anticipates claim 3.

Defendants expect Vanda to argue that Defendants' labels will induce infringement of the RE604 patent because some prescribers following the instructions in Defendants' proposed labels will necessarily entrain blind patients with Non-24. As Vanda's infringement expert Dr. Combs put it, "if you're giving

tasimelteon as directed, it's going to lead to entrainment." Tr. 214:5-11; *cf. AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (finding that label induced infringement based in part on evidence that language on the label "would inevitably lead some consumers to practice the claimed method"). Vanda's counsel put the matter even more bluntly: "[I]n our view, the -- you can't treat Non-24 with tasimelteon without being covered by at least one of these patents; specifically the reissued patent." Tr. 1224:13-16. Vanda's theory fails on both the facts and the law, as Defendants will explain in their responsive briefs.

But, even if Vanda were right, it would still lose on this patent, because claim 3 would be anticipated by the Clinical Trials reference. *See* DTX-42. That is because the dosing regimen on Defendants' proposed labels tracks exactly the dosing regimen set forth in the prior-art clinical trial protocol. Thus, if the labels inevitably lead to practicing the claims, the clinical-trial protocol does too—which means it anticipates. This is a textbook example of the principle that "[t]hat which infringes, if later, would anticipate, if earlier." *Peters v. Active Mfg. Co.*, 129 U.S. 530, 537 (1889).

(a) Clinical Trials qualifies as prior art under 35 U.S.C. § 102(b) because it was publicly available as of July 2010, more than one year before the priority date of the RE604 patent.

The evidence at trial showed that the original version of the Hetlioz Phase III trial protocol—the substance of which is found at DTX-42.9-11—was publicly

posted on clinicaltrials.gov July 2010, more than one year before the priority date of the RE604 patent. That makes Clinical Trials prior art under 35 U.S.C. § 102(b) (pre-AIA). *See Jazz Pharms., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1355 (Fed. Cir. 2018) (online information is publicly accessible if it is "made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.").[9]

Clinicaltrials.gov is a government website on which clinical trials sponsors are required to post their clinical study protocols and results. The website contains a "History of Changes" feature that allows the user to see when a given "record was updated and how it was changed." Tr. 786:12-16 (Emens); *see* https://clinicaltrials.gov/ct2/help/how-read-study#Historical. According to the History of Changes section of the record for the Hetlioz Phase III trial, the first version of the protocol was posted online on July 15, 2010. Tr. 779:15-780:7, 787:2-12 (Emens). The July 2010 version is accessible at https://clinicaltrials.gov/ct2/history/ NCT01163032?V_1=View#StudyPageTop. The Court judicially noticed this webpage at trial, *see* Tr. 795:9-796:5, as permitted by Third Circuit precedent, *see Vanderklok v. United States*, 868 F.3d 189, 205 (3d Cir. 2017). And Dr. Emens explained in unrebutted testimony that the contents of

[9] DTX-42 is a compilation of various updates to the Hetlioz clinical trial protocol. Tr. 778:4-13 (Emens). The first version of the protocol found at DTX-42.9-11 is the relevant one for purposes of Defendants' invalidity argument.

that version are accurately reflected by the contents of DTX-42.9-11. *See* Tr. 790:17-793:6 (Emens).[10] Accordingly, the July 2010 version of the protocol qualifies as prior art.

(b) Vanda's Clinical Trial Protocol expressly discloses the dosing regimen of claim 3.

Claim 3 of the RE604 patent recites, in essence, a dosing regimen and a result. The dosing regimen comprises administration of (i) 20 mg tasimelteon (ii) 0.5 to 1.5 hours before bedtime to (iii) a Non-24 patient who (iv) is totally blind. JTX-1.41 (claims 1, 2, 3). The result is that the patient (i) becomes entrained "to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours" and (ii) "maintain[s]" that entrainment. *See id.*

At trial, Dr. Emens demonstrated that each element of the dosing regimen is found in the Clinical Trials document: the protocol discloses administering 20 milligrams tasimelteon to totally blind Non-24 patients one hour before bedtime. Tr. 816:4-817:10 (Emens); *see* DTX-42.9 (describing a study "to investigate the

[10] During the colloquy following Vanda's evidentiary objection to the Clinical Trials document, counsel for Vanda pointed out that the successive versions of the protocol found in DTX-42 have appended to them a citation to the 2015 article in which the results of the Phase III trial were published. As the Court observed, however, the evidence showed that the 2015 article was "automatically indexed" to the clinicaltrials.gov website (including to portions of the website displaying the protocol as it existed prior to 2015). Tr. 797:15-22; *see* Tr. 778:22-779:7, 780:8-16 (Emens); DTX-42.11.

efficacy and safety of 20 mg tasimelteon versus placebo in totally blind subjects with N24HSWD"); DTX-42.10 (disclosing that patients would receive tasimelteon "approximately 1 hour prior to their target bedtime").

(c) Vanda's clinical trial protocol inherently discloses the remaining limitation of the RE604 patent.

Vanda's clinical trial protocol does not disclose the results recited in claim 3—the "entraining" and "maintaining" limitations. (Indeed, it could not disclose the results, because the study had not been performed yet.) But, if Vanda were correct that following the administering steps in Defendants' labels will inevitably lead to infringement of the "entraining" and "maintaining" limitations, then it follows that Vanda's clinical trial protocol inherently discloses these two limitations.

A prior-art reference inherently discloses a claimed limitation if that limitation "is necessarily present, or inherent" in the reference. *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012). As relevant here, if the limitation at issue requires a specific therapeutic outcome (like entraining), the limitation is "necessarily present[] or inherent" in a reference describing steps that "inevitably result" in that therapeutic result. *Id.* In *Montgomery*, for example, the claim recited (i) administering ramipril to stroke-prone patients and (ii) the therapeutic outcome of preventing or treating a stroke. *Id.* The "HOPE" reference (as it happens, a clinical trial protocol) explicitly disclosed administration of ramipril to stroke-

prone patients. *See id.* The issue was whether, by expressly disclosing this step, the protocol also *inherently* disclosed the *result* of preventing or treating a stroke. The Federal Circuit said yes: "HOPE discloses a protocol for the administration of ramipril to stroke-prone patients, and administering ramipril to stroke-prone patients inevitably treats or prevents stroke. Thus, HOPE inherently anticipates the claims at issue." *Id.* at 1381; *see also King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275–76 (Fed. Cir. 2010) (claim requiring "increasing the oral bioavailability of metaxalone" by administering metaxalone with food was inherently anticipated by prior-art disclosure of "taking metaxalone with food" because "the natural result of taking metaxalone with food is an increase in the bioavailability of the drug").

If Vanda's infringement position were accepted, the same result would follow here. Dr. Emens's unrebutted testimony established that Vanda's clinical trial protocol discloses the exact same administration steps that the labels recite. *See* Tr. 817:16-818:19 (Emens); *compare* DTX-42.9-10 (Clinical Trials), *with* JTX-28.1, 12 (tasimelteon drug label). If practicing these steps today would invariably lead to direct infringement of claim 3 of the RE604 patent, then a 2010 disclosure of those same steps would inherently anticipate that claim. *See Peters*, 129 U.S. at 537.

C. Claim 5 of the ’487 patent is invalid.

1. Claim 5 is invalid as obvious over (a) Lankford, Hack, and the ’244 publication and (b) Hardeland, Hack, and the ’244 publication.

Claim 5 of the ’487 patent recites a method of treating a Non-24 patient by orally administering 20 mg tasimelteon “without food.” JTX-5.4 (claims 1, 4, 5). Administering 20 mg tasimelteon to treat Non-24 would have been obvious over Lankford, Hack, and the ’244 publication; and Hardeland, Hack, and the ’244 publication for the reasons discussed above. Claim 5 adds only that the administration occur “without food,” which, under the Court’s construction, means “the patient has not consumed food within 30 minutes prior to administration of tasimelteon and does not consume food with the administration of tasimelteon.” D.I. 183 at 3.

As Dr. Emens explained, the “without food” limitation would also have been obvious in light of the same two combinations of prior art. Tr. 823:7-824:7 (Emens). The prior art is replete with disclosures of patients receiving tasimelteon 30 minutes before bedtime. *See* DTX-16.6 (Hardeland); DTX-20.5 (Lankford); DTX-41.24 (’244 publication); *see also* Tr. 823:11-19 (Emens). And, given that administration protocol, “it’s more likely than not that they wouldn’t have had any food on board.” Tr. 823:14-18 (Emens).

Indeed, there were in effect only two choices for the prior-art administration of tasimelteon: it could be taken with food or without food. Tr. 823:19-23 (Emens). And, "among those limited options, a skilled artisan had ample reason to avail himself of the obvious option of" administering the drug without food. *C.R. Bard, Inc. v. Medline Indus., Inc.*, 2021 WL 3574043, at *4 (Fed. Cir. Aug. 13, 2021) ("When two equally viable options are available, as here, then, without more, either one would seem to have been obvious."). Specifically, since most people do not eat right before they go to bed (particularly those consciously using a protocol to manage their sleep), administration without food would be the logical choice for a drug taken shortly before bedtime. *See also* Tr. 823:19-23 (Emens); *Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1350 (Fed. Cir. 2020) (finding claim to a two-stage turbine obvious because the prior art presented "a binary choice" between one-stage turbines and two-stage turbines). Moreover, the fact that the prior art does not "expressly describe" administration without food is irrelevant; "obviousness requires no such express disclosure." *C.R. Bard*, 2021 WL 3574043, at *4-5 (claimed medical procedure kit that required storage of two syringes in a single compartment was obvious because there were only two options available: storing the syringes together or storing them separately).

Dr. Emens' testimony on this point went essentially unrebutted. Vanda's expert Dr. Czeisler mentioned the '487 patent only in passing, and he made only

two points: (i) "the circadian drive for hunger peaks…late in the evening"; and (ii) "one out of five people eat a full meal in the hour before they go to bed." Tr. 1184:18-1185:24 (Czeisler). But, even if accepted at face value, these two propositions do nothing to undermine the common-sense conclusion that *most* people who take a drug shortly before bedtime would take that drug at least 30 minutes after eating. After all, if one out of five people eat a meal within an hour before bedtime, four out of five people do not. And, in any event, the proportion of patients who eat shortly before bedtime is in the end irrelevant: the point is that, "[w]hen two equally viable options are available," *both* options are obvious. *C.R. Bard*, 2021 WL 3574043, at *4.

2. If the Court finds that claim 5 requires that administration of tasimelteon without food be more effective at treating Non-24 than administration of tasimelteon with food, the claim is invalid for lack of written description.

Claim 5 of the '487 patent recites a method of treating Non-24 by administering 20 mg/d tasimelteon without food. JTX-5.4 (4:2-6, 13-16). On its face, claim 5 does not require that administering tasimelteon without food is better at treating Non-24 than administering it with food. Tr. 824:20-24 (Emens). Nonetheless, at trial, Vanda's Dr. Polymeropoulos testified that Vanda invented a method of administering tasimelteon without food that is more effective at treating Non-24 than if tasimelteon were administered with food. Tr. 825:5-12 (Emens); Tr. 138:9-139:11 (Polymeropoulos).

If the Court were to agree that such an invention is claimed in the '487 patent, the claim would be invalid for lack of written description. *See generally* 35 U.S.C. § 112. The specification of the '487 patent does not support Vanda's assertion that administering tasimelteon without food is more effective at treating Non-24 than administering it with food. Tr. 825:13-826:1 (Emens); *see also* JTX-5. Indeed, the '487 patent only discloses the effects of administering tasimelteon to *sighted healthy individuals* with or without food. Tr. 826:14-18 (Emens); Tr. 186:21-187:3 (Polymeropoulos) (admitting that the food-effect study that Vanda did with tasimelteon was in healthy volunteers); *see also* JTX-5. Further, while the '487 patent incorporates the specification of the RE604 patent, the RE604 patent likewise does not include studies that evaluate the effect of administering tasimelteon with and without food to Non-24 patients. Tr. 826:20-827:18 (Emens); *see also* JTX-5.3; JTX-1. To this point, Dr. Polymeropoulos admitted that the SET and RESET studies—*i.e.*, those studies disclosed in the RE604 patent—did not study the effect of food on the administration of tasimelteon. Tr. 189:6-8 (Polymeropoulos). Further, as Dr. Emens explained, without a head-to-head trial where tasimelteon is administered with food to a group of Non-24 patients and without food to a group of Non-24 patients, it is not possible to demonstrate that tasimelteon is more effective at treating Non-24 when administered without food versus with food. Tr. 827:19-828:3 (Emens). It is

undisputed that such information is not present in the ’487 patent. *See generally* JTX-5.

In other words, a skilled artisan reading the specification of the ’487 patent would not think that the inventors possessed an invention that includes improving efficacy in treating Non-24 by administering tasimelteon without food. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (written description must reasonably convey “to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.”); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002) (patent may not claim an invention that is broader than the disclosure of the specification). Accordingly, claim 5 of the ’487 patent is invalid for lack of written description if it requires improved efficacy in treating Non-24 with tasimelteon without food versus treating Non-24 with tasimelteon with food. Tr. 825:13-21 (Emens).

D. Claim 14 of the ’829 patent is invalid as obvious over (a) Lankford, Hack, the ’244 publication, and Hardeland; and (b) Hardeland, Hack, and the ’244 publication.

Claim 14 of the ’829 patent recites a method of treating a non-24 patient who is taking a strong CYP1A2 inhibitor by “discontinuing treatment with the strong CYP1A2 inhibitor” and then administering 20 mg tasimelteon. JTX-3.35 (claims 13, 14). As just explained, Dr. Emens’ testimony establishes that treating Non-24 by administering 20 mg tasimelteon would have been obvious in view of

Lankford, Hack, and the ’244 publication, as well as Hardeland, Hack, and the ’244 publication. And, for the reasons explained by Dr. Greenblatt, the additional limitation added by claim 14—the requirement that administration of a strong CYP1A2 inhibitor be discontinued before starting tasimelteon—would have been obvious in view of Hardeland.

Hardeland discloses that “tasimelteon was primarily metabolized by the CYP1A2… isoenzyme[].” DTX-16.4 (citing Vachharajani); Tr. 1036:3-16, 1049:3-25, 1100:2-9 (Greenblatt). And Hardeland explicitly states that because “tasimelteon is metabolized by the CYP isoenzymes 1A2…coadministration of any drug that inhibits one of these isoenzymes *should be regarded with caution*.” DTX-16.6 (emphasis added); Tr. 1049:3-1050:9, 1067:17-20, 1069:7-22 (Greenblatt).

A POSA intending to administer tasimelteon to a subject already taking a CYP1A2 inhibitor would have heeded the warning in Hardeland. That is particularly so given the background knowledge that ramelteon—a melatonin agonist “closely related to tasimelteon”—is metabolized by CYP1A2, is known to have a large drug-drug interaction with strong CYP1A2 inhibitors, such as fluvoxamine, and that, as a result of this drug-drug interaction, it is recommended that ramelteon should not be co-administered with certain CYP1A2 inhibitors such as fluvoxamine. Tr. 1037:5-6, 1038:25-1039:6, 1040:6-23, 1043:18-1046:3,

1116:24-1117:13 (Greenblatt); Tr. 1156:6-10 (Parkinson); JTX-93.4; DTX-16.2; JTX-35.2, 35.8, 35.10; JTX-92.1; DTX-28.9.

Further, for the same reasons stated above for claim 3 of the RE604 patent, a skilled artisan would have been motivated to combine Lankford, Hack, the '244 publication, and Hardeland and Hardeland, Hack, and the '244 publication by reading the references themselves. A clinical study would not have been required for a skilled artisan to heed the warning in Hardeland to exercise caution in coadministering tasimelteon with a CY1A2 inhibitor. Given that it was known that CYP1A2 metabolized tasimelteon, based on common sense, a POSA would have reasonably expected that discontinuing the treatment with the strong CYP1A2 inhibitor before treating the patient with tasimelteon would avoid the potential drug-drug interaction. While a clinical drug-drug interaction study would give a definitive answer as to whether there is a drug-drug interaction between tasimelteon and a CYP1A2 inhibitor, the law does not require a certainty of success. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."); *see also Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020).

In short, the explicit teachings of Hardeland, in view of the background knowledge of a skilled artisan, would have made it obvious to discontinue

administering a strong CYP1A2 inhibitor prior to treating a patient with tasimelteon.

E. Claim 4 of the '910 patent is invalid as obvious over (a) Lankford, Hack, the '244 publication, and Pandi-Perumal; and (b) Hardeland, Hack, the '244 publication, and Pandi-Perumal.

Claim 4 of the '910 patent requires treating Non-24 in a light-perception impaired patient who is taking rifampicin by "discontinuing the rifampicin treatment" and then administering 20 mg tasimelteon once daily before a target bedtime. JTX-4.41 (claims 1, 2, 3, 4). As explained above, Dr. Emens' testimony establishes that treating blind (*i.e.*, light-perception impaired) Non-24 patients by administering 20 mg tasimelteon before bedtime would have been obvious in view of Lankford, Hack, and the '244 publication, as well as Hardeland, Hack, and the '244 publication. And Dr. Greenblatt's testimony shows that the additional limitation added by claim 4—discontinuing treatment with rifampicin before administering tasimelteon—would have been obvious in view of Pandi-Perumal.

Pandi-Perumal taught that ramelteon is metabolized by CYP3A4. JTX-93.4; Tr. 1038:16-1039:13 (Greenblatt); Tr. 1156:6-10 (Parkinson); *see also* JTX-35.2, 35.10; JTX-92.1. Further, Pandi-Perumal discloses that rifampin—the strongest known CYP3A4 inducer—interacts with ramelteon. JTX-93.4; Tr. 1043:10-17, 1046:5-7, 1050:20-1051:11, 1116:24-1117:13 (Greenblatt); *see* JTX-35.10. Pandi-Perumal also discloses that the "CYP inducer rifampicin has been shown to

considerably decrease levels of…ramelteon…[thus] to avoid losses in efficacy, this and other strong upregulators of relevant CYP enzymes should be avoided." JTX-93.4; Tr. 1050:20-1051:11, 1116:24-1117:13 (Greenblatt); *see also* JTX-35.10.

Further, as explained above, as of the priority date, a skilled artisan would have had strong reasons to expect that tasimelteon would similarly interact with rifampin. A skilled artisan would have recognized that ramelteon is a melatonergic drug "closely related to tasimelteon." Tr. 1037:5-6 (Greenblatt); JTX-93.1-2; DTX-16.2. Indeed, as Dr. Greenblatt testified, much like tasimelteon, ramelteon was known to bind to, and have high affinity for, melatonin MT1 and MT2 receptors, and have a relatively short half-life. JTX-35.1; DTX-16.3; JTX-93.2; JTX-92.2; Tr. 1035:7-18, 1037:5-13, 1040:6-19 (Greenblatt). Further, the prior art disclosed that tasimelteon and ramelteon are structurally similar, sharing a dihydrobenzofuran structure and the propanamide residue. DTX-16.3-16.4; Tr. 1040:6-22, 1108:8-18 (Greenblatt).

Armed with the background knowledge that CYP3A4 metabolizes small molecules, such as tasimelteon, a "very, very large percentage" of the time, Tr. 1146:19-1147:6 (Parkinson), the known similarities between tasimelteon and ramelteon, and the disclosures in Pandi-Perumal concerning the metabolism of ramelteon and its known interaction with the strongest known CYP3A4 inducer, rifampin, a skilled artisan would have found it obvious to discontinue

administering the CYP3A4 inducer rifampin prior to treating a patient with tasimelteon. Tr. 1047:23-1048:19, 1050:20-1052:2, 1104:4-25 (Greenblatt); *see also* Tr. 485:11-486:2 (Feeney) (describing internal Vanda document noting that information about ramelteon's metabolism was part of the rationale for Vanda's DDI studies on tasimelteon); *In re Merck & Co.*, 800 F.2d 1091, 1096-97 (Fed. Cir. 1986); *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384-85 (Fed. Cir. 2018) ("Where the patent is directed to a new treatment using a known compound it is reasonable to assume that similar compounds that share certain common properties are apt to share other related properties as well.") (citing *Merck*, 800 F.2d at 1096).

This same background knowledge—especially given the known similarities between tasimelteon and ramelteon—would have motivated a POSA to combine Pandi-Perumal with Lankford, Hack, the '244 publication; and Hardeland, Hack, the '244 publication. Additionally, because Hardeland taught that tasimelteon is a structural analog of ramelteon, known to exert its effects through the same MT1 and MT2 receptors, a POSA would have reasonably expected that tasimelteon, like ramelteon, was a substrate of CYP3A4. DTX-16.2-16.4; Tr. 1035:7-18 (Greenblatt). Moreover, Pandi-Perumal taught that rifampicin "considerably decrease[d] levels of…ramelteon" when coadministered. JTX-93.4; Tr. 1051:3-11. Accordingly, a POSA would have reasonably expected that discontinuing

treatment with rifampicin prior to treating the patient with tasimelteon would avoid the use of tasimelteon in combination with rifampicin, thereby successfully avoiding reduced exposure to tasimelteon caused by rifampicin-mediated induction of CYP3A4.

CONCLUSION

The Court should enter judgment that the asserted claims of the patents-in-suit are invalid.

/s/ Kaan Ekiner
Thomas Francella (No. 3835)
Kaan Ekiner (#5607)
COZEN O'CONNOR
1201 North Market Street, Suite 1001
Wilmington, DE 19801
(302) 295-2025
tfrancella@cozen.com
kekiner@cozen.com

OF COUNSEL:
Barry P. Golob
W. Blake Coblentz
Aaron S. Lukas
COZEN O'CONNOR
1200 Nineteenth Street N.W.
Washington, DC 20036
(202) 912-4800

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com

Keri L. Schaubert
COZEN O'CONNOR
3 WTC, 175 Greenwich Street,
55th Fl. New York, NY 10007
(212) 509-9400
Attorneys for Defendants Apotex Inc. and Apotex Corp

OF COUNSEL:
J.C. Rozendaal
Deirdre M. Wells
William H. Milliken
Sasha Rao
Michael Bruns
Byron L. Pickard
STERNE, KESSLER, GOLDSTEIN
& FOX P.L.L.C.
1100 New York Avenue, N.W., Suite 600
Washington, DC 20005
(202) 371-2600
Attorneys for Defendant Teva Pharmaceuticals USA, Inc

Dated: April 26, 2022

CERTIFICATE OF COMPLIANCE

I hereby confirm that this document complies with the type and number limitations set forth in the Court's November 6, 2019 Standing Order and the Stipulation and Order Regarding Post-Trial Briefing (D.I. 305). I certify that this document contains 9,750 words, which were counted using the word count feature in Microsoft Word, in 14-point Times New Roman font. The word count does not include the cover page, tables, or the counsel blocks.

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.